SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ultraviolet-Absorbing Anterior Chamber Phakic Intraocular Lens (PIOL)

Device Trade Name: ARTISAN® Phakic Lens (Models 204 and 206) also known as Verisyse™ Phakic Lens (ModelsVRSM5US and VRSM6US)

Applicant's Name and Address: Ophtec USA, Inc.
6421 Congress Avenue
Suite #112
Boca Raton, FL 33487

Date of Panel Recommendation: February 5, 2004

Premarket Approval Application (PMA) Number: P030028

Date of Notice of Approval to Applicant: September 10, 2004

II. INDICATIONS FOR USE

The ARTISAN® Myopia Intraocular Lenses (IOLs) are indicated for:

- the reduction or elimination of myopia in adults with myopia ranging from -5 to -20 diopters with less than or equal to 2.5 diopters of astigmatism at the spectacle plane and whose eyes have an anterior chamber depth greater than or equal to 3.2 millimeters; and,

- patients with documented stability of refraction for the prior 6 months, as demonstrated by spherical equivalent change of less than or equal to 0.50 diopters.

III. CONTRAINDICATIONS

The ARTISAN® Phakic IOL is contraindicated in patients:

- Who are less than 21 years old
- With an anterior chamber depth (ACD) less than 3.2 mm
- With abnormal irises, such as peaked pupil or elevated iris margin
- Who are pregnant or nursing
- Who do not meet the minimum endothelial cell density

Table 1: Endothelial Cell Density

Age Range (years)	Minimum Endothelial Cell Density (cells/mm^2)
21-25	3550
26-30	3175
31-35	2825
36-40	2500
41-45	2225
>45	2000

Table 1 displays the minimum endothelial cell density per age group at time of implantation. The table was developed using a rate of 2.31% (the upper 90% confidence interval of the average cell loss for eyes with ACDs of 3.2 mm or greater.) It sets the minimum endothelial cell density criteria as a function of age that should result in at least 1000 cells/mm^2 at 75 years of age. The patient's ECD should be monitored periodically at the physician's discretion.

IV. WARNINGS AND PRECAUTIONS

The warning and precautions can be found in the ARTISAN® labeling.

V. DEVICE DESCRIPTION

The ARTISAN® Phakic Lens is a single-piece lens manufactured from Perspex CQ-UV, ultraviolet light absorbing polymethylmethacrylate (PMMA). The lens is designed for implantation into the anterior chamber of a phakic human eye (an eye that has its natural lens) for the correction of high myopia between -5 D and -20 D. The lens has either a 5.0 mm (Model 206) or 6.0 mm (Model 204) convex-concave optic that is incorporated into an 8.5 elliptically-shaped plate lens design. The lens has two enclavation arms on either side for fixation to the relatively immobile mid-peripheral iris stroma. The lens has a slight anterior vault to provide adequate space for aqueous flow and avoid iris chaffing. Lens Model 206 is available in one diopter increments from -5 D to -20 D and is intended for subjects with pupil sizes up to 6.0 mm in low light. Due to the larger optic size, Model 204 is available in one diopter increments from -5 D to -15 D, instead of -20D as for Model 206.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The procedures used in the treatment of myopia are spectacles, contact lenses, laser in situ keratomileusis (LASIK), automated lamellar keratoplasty (ALK), radial keratotomy (RK), and photorefractive keratotomy (PRK).

VII. MARKETING HISTORY

The ARTISAN® Phakic IOL has been marketed in over 40 countries to date. The ARTISAN® Phakic IOL has not been withdrawn from any market for reasons relating to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The major adverse events (AEs) experienced during the ARTISAN® Phakic clinical trial were IOL dislocation (0.8%), retinal detachment (0.6%), and surgical reintervention (4.2%). These rates were higher or the same as the rates observed in the historical control population (also known as the FDA grid). The other adverse event rates were lower than the incidence reported in the historical control population.

Table 2: Comparison of Adverse Events Rates Reported at 12 Months

Adverse Event	Cumulative % (n/N)	FDA Grid %	Persistent % (n/N)	FDA Grid %
Endophthalmitis	0	0.1	–	–
Hyphema	0.2 (1/662)	2.2	–	–
Hypopyon	0	0.3	–	–
IOL Dislocation	0.8 (5/662)*	0.1	–	–
Cystoid Macular Edema	0	3.0	0 (0/232)	0.5
Pupillary Block	0	0.1	–	–
Retinal Detachment	0.6 (4/662)+	0.3	–	–
Surgical Reintervention	4.2 (28/662)▽	0.8	–	–
Corneal Edema	–	-	0	0.3
Iritis	0.5(3/662)Δ	-	0	0.3
Raised IOP Requiring Treatment	–	-	0	0.4
Surgical Treatments Not Monitored in the FDA Grid				
Preventative Lens Repositioning	2.1 (14/662)	–	–	–
Refractive Procedures**	2.6 (17/662)	–	–	–
Nd:Yag Peripheral Iridotomy	3.0 (20/662)	–	–	–
Aqueous Release	1.8 (12/662)	–	–	–
Resuture Wound Leak	1.2 (8/662)	–	–	–

*Four events due to inadequate surgical fixation; one event due to blunt trauma

▽Surgical reintervention include: lens explant (10/28), lens exchange (9/28), lens reattachment (5/28) and retinal detachment (4/28).

ΔThere is no FDA Grid value for cumulative iritis

+ Comparison should be made to literature for retinal detachment rates for high myopes:

- Retinal detachment rates increase with increasing myopia[1]
  The risk of retinal detachment within one year of implantation of this device is 0.6%. The risk of retinal detachment for high myopes following implantation is more than 10 times the risk without surgery, i.e. greater than 10-fold the background rate of retinal detachment for high myopes (greater than minus 3 diopters).
- 5.0% in myopic eyes > 6 D[2]
- 0.8% to 7.5% in pseudophakic eyes with high axial myopia[3]

[1]Ogawa, A and Tanaka, M. The relationship between refractive errors and retinal detachment, Jpn J. Ophthalmology 32:310; 1988.
[2]Dellone-Larkin G, Dellone CA. Retinal detachment. Available at http://www.emedicine.com/emerg/topic504.htm. Accessed January 13, 2004.
[3]Jacobi, F and Hessemer, V. Pseudophakic retinal detachment in high axial myopia, J. Cat. Refract Surg 23:1095, 1997.

**Refractive procedures include: LASIK (11/17); AK (3/17); LRI (2/17) and PRK (1/17).

IX. SUMMARY OF PRECLINICAL STUDIES

Ophtec performed nonclinical studies on the ARTISAN® IOL in accordance with the FDA guidance document for testing intraocular lenses dated October 10, 1997. Additionally, manufacturing and sterilization site inspections were used to establish the adequacy of the manufacturing process. Nonclinical testing demonstrated the ARTISAN® Phakic lens' safety and effectiveness from microbiology, toxicology, engineering, and manufacturing perspectives. Summaries of the non-clinical test conducted are listed below by discipline.

Biocompatibility

The ARTISAN® Phakic IOL is made from polymethy-methacrylate (PMMA) Perspex CQ-UV (ICI Chemical Co., England). The material has a proven history of over 50 years for use as an IOL material. Ophtec conducted a battery of acute and chronic *in vivo* and *in vitro* toxicity tests to establish the PMMA's biocompatibility profile. FDA waived some biocompatibility tests because Ophtec provided sufficient justification.

Biocompatibility Test	Test Result	Conclusion
Cytotoxicity – agar diffusion, direct contact	Test received waiver	–
Cytotoxicity – agar diffusion, indirect contact	Test received waiver	–
Cytotoxicity – MEM elution	No cell lysis or growth inhibition	Noncytotoxic
Cytotoxicity – inhibition of cell growth	Test received waiver	–
Genotoxicity – Ames Salmonella/Microsome	Number of revertant in test similar to negative control	Nonmutagenic Noninhibitor
Maximization Sensitization	No erythema or edema	Nonsensitizing
Nonocular implant – 4 weeks	Slight fibrosis and inflammation	Nonirritant
Ocular Implant	Test received waiver	–

Engineering

Test	Objective	Result
Anatomical clearance	To determine minimum theoretical anatomical clearance under worst	Characterized the amount of clearance

analysis	case conditions	
Surface contamination	To determine the residual levels from the manufacturing process	No residuals detected above the detection limits of the methods used
Exhaustive extraction	To determine levels of unreacted monomers in the finished device	Level of methyl-methacrylate was ~0.5%.
Optical characterizat-ion	To determine the characteristic optical performance of the design using powers spanning the available range	In the ISO eye model described in 11979-2, the MTF values at 1/3 of the diffraction limit were greater than 70% of the diffraction limited curve value at that spatial frequency
Sterilization residuals	To determine the levels of residuals remaining on the final device after sterilization and aeration.	The levels below those listed in ANSI Z80.7: 2002.
Dimensions	To determine variation in manufactured lenses	The variations within the specifications listed in 11979-3.
Packaging and shipping	To determine if the packaging is adequate to protect the device during shipping	All lenses were undamaged after simulated shipping.
Photostability	To determine the stability of the material to UV radiation	Followed the protocols in 11979-5. No damage to the lens was observed.
Hydrolytic stability	To determine the hydrolytic stability of the material	Followed the protocols in 11979-5. No damage to the lens was observed.

Microbiology

- The ethylene oxide sterilization cycle was validated according to ISO 1113 and EN 556. Three half cycles and one sublethal cycle were run and the sterility testing demonstrated that all biological indicators were killed in the sterilization process and thus assuring that a full cycle would achieve a sterility assurance level of 10^{-6}.

- Bacterial endotoxin testing was conducted by the limulus amebocyte lysate (LAL) gel clot method and there results meet the FDA limits for endotoxins on medical devices (≤20 endotoxin units/device).

- Seal strength and burst tests were conducted on the packaging to evaluate the package integrity. The packaging met the seal strength (180 to 400 mbar) and burst strength (180 to 400 mbar) passing criteria.

- Ethylene oxide (EO) residual levels on the ARTISAN® IOL was determined using the headspace analysis method. The EO levels meet the ISO 10993-7 limits of 1.25 microgams EO per lens.

- To determine the microbial integrity of the packaging, seal integrity and sterility

testing of the packaged IOL was conducted. The aged packaging met the seal strength (180 to 400 mbar) passing criteria and sterility testing of the aged IOLs reported that all IOLs remained sterile.

- Microbiological testing is performed on the ARTISAN® IOL prior to final product release. Final product testing consists of the following: LAL gel clot method, sterility testing of biological indicators from the sterilization load and routine sterilization chamber control.

X. SUMMARY OF CLINICAL STUDIES

The objective of the clinical study was to assess the safety and effectiveness of the ARTISAN® Phakic IOL for the reduction or elimination of myopia in adults with myopia ranging from greater than -5 D to less than -20 D with less than or equal to 2.5 D of astigmatism at the spectacle plane and whose eyes have an anterior chamber depth greater than or equal to 3.2 mm.

Study Design

Ophtec conducted a three-year prospective, non-randomized clinical study to investigate the safety and efficacy of the ARTISAN® / Verisyse™ phakic intraocular lens. A total of 684 patients enrolled in the study; 495 of these patients had the fellow eye implanted. The primary analysis cohort was 662 first eyes implanted. Patients with protocol deviations were included in the primary analysis cohort unless they had keratoconus or preoperative best spectacle corrected visual acuity (BSCVA) worse than 20/40. A total of 232 first implanted eyes (371 first and second eyes) reached the 3-year follow-up visit.

Subjects were selected from the normal patient population at each of the investigational sites according to the inclusion and exclusion criteria below. The same inclusion and exclusion criteria also applied to fellow eyes that were implanted as well.

Inclusion Criteria:

- Ages 21 to 50
- Visual disabling, myopia between -5 D and -20 D
- Stable manifest refraction (+ 0.5 D at two exams one month apart)
- Unsatisfactory vision with contact lenses or spectacles
- General good health
- Willing and able to comply with postoperative evaluation schedule
- Signed informed consent

Exclusion Criteria:

- Any form of cataract preoperatively or a predisposition toward cataract development
- Patients with myopia less than -5 D or greater than -20 D
- Patients not able to meet extensive postoperative evaluation requirements
- Mentally retarded patients
- Patients with significant amounts of astigmatism (>2.5D)
- Patients with retinal detachment or a family history of retinal detachments
- Patients with Stargardt's retinopathy
- Patients with an abnormal pupil
- Patients with an abnormal iris
- Patients with an abnormal cornea
- Patients with gastric ulcers or diabetic mellitus (if high doses of postoperative corticosteroids are required)
- Patients with endothelial cell counts less than 2000 cells/mm^2
- Patients with an anterior chamber depth less than 3.2 mm
- Patients with glaucoma or a family history of glaucoma
- Surgical difficulty at the time of surgery which might increase the potential for complications
- Abnormality of the iris or ocular structure which would preclude fixation, such as aniridia, hemi-iridectomy, severe iris atrophy or microphthalmos
- Chronic or recurrent uveitis or history of the same
- Proliferative diabetic retinopathy
- Rubeosis iridis
- Severe iris atrophy or other compromising iris pathology
- Endothelial corneal dystrophy or family history of corneal dystrophy
- When the patient has no useful vision or vision in the fellow eye
- High preoperative intraocular pressure, 21 mmHg
- Prior IOL or corneal surgery
- Preexisting macular degeneration or macular pathology that may complicate the ability to assess the benefit or lack of benefit obtained by the lens
- Patients that, when examined preoperatively, are not expected to achieve a postoperative visual acuity of 20/40 or better
- Patients under the age of 21 or older than 50
- Fixed pupil size greater than 4.5mm
- Low light pupil size greater than lens optic size: 5.0 mm (for lens Model 206) or 6.0 mm (for lens Model 204)

Patient Accountability

The one-year visit was the major time point for the majority of the safety and effectiveness endpoints. Patient accountability for treated first eyes at the one-year post-operative visit was 74.5% (493/662). At the two-year visit and three-year visit, compliance was 53.5% (354/662) and 35% (232/662). Of the discontinued subjects at the one-year visit, the majority were lost to follow-up (72.6%, 53/73; moved, withdrew consent, unable to locate or no response from subject) and the rest were lens removal or exchanges (15.1%, 11/73) or death from device unrelated causes (2.7%, 2/73).

Patient Assessments

Table 3: Summary of Examinations Required at Each Visit

Examination	Pre-Op	Op	PO1 1-6 days	PO2 2-3 wks	PO3 4-8 wks	PO4 4-6 mos	PO5 7-11 mos	PO6 12-14 mos	PO7 18-24 mos	PO8* 34-38 mos
Medical History, Inclusion/Exclusion Criteria	X									
Informed Consent	X									
Targeted refraction/inlay power calculation	X									
Method of correction used	X		X	X	X	X	X	X	X	X
Uncorrected Distance VA	X		X	X	X	X	X	X	X	X
Uncorrected Near VA	X		X	X	X	X	X	X	X	X
Manifest Refraction	X		X	X	X	X	X	X	X	X
Best Corrected Distance VA with MR	X		X	X	X	X	X	X	X	X
Cycloplegic Refraction	X					X		X	X	X
Best Corrected Distance VA with CR						X		X	X	X
Mesopic Pupil Size	X									
Slit Lamp Exam*	X		X	X	X	X	X	X	X	X
Corneal Status	X		X	X	X	X	X	X	X	X
IOL Position			X	X	X	X	X	X	X	X
Pupil Shape			X	X	X	X	X	X	X	X
Dilated Fundus Exam[+]	X					X		X	X	X
Condition of Natural Lens	X					X		X	X	X
Anterior Chamber Depth & Keratometry	X									
Intraocular Pressure	X		X	X	X	X	X	X	X	X
Endothelial Cell Count	X					X		X	X	X
Optical/Visual Symptoms			X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Ophthalmic Medications		X	X	X	X	X	X	X	X	X
General Operative Procedures		X								
Other/Additional Surgical Procedures		X								

* Original protocol did not require PO8, this visit was added after the initiation of the clinical trial
**Biomicroscopic slit-lamp exam includes determination of any medical or lens complications
[+]Dilated fundus exam for determination of the condition of natural lens, retinal status, and ocular pathology/complications.

Table 3 summarizes the study subject's visit schedule and the tests performed at each visit.

Demographic Data

Analysis of the first eye patient demographic reveal an approximately equal number of left (52.3%; 346/662) and right eyes (47.7%), a preponderance towards female gender

(64.5%; 427/662), although there was no difference in the safety and effectiveness of the device based on gender, and 85.0% Caucasian with 6.2% Asian, 3.2% Black, and 4.1% Hispanic patients. The majority of eyes had either brown (44.9%; 297/662) or blue (33.5%; 222/662) iris color. The patients' mean age was 39.6 years at the time of surgery with the majority between 21 and 50 years of age. The overall mean diopter power implanted was -12.6 D (SD=2.7) within a range of -5.0 D to -20.0 D. The mean diopter power for Model 204 was -11.9 D (SD=2.2) while the mean diopter power for Model 206 was -15.5 D (SD=2.8) as a result of the larger diopter range for Model 206.

Data Analysis and Results

Efficacy Analysis

The postoperative results demonstrated that the ARTISAN® Phakic IOL provided correction for high myopia. The visual acuities at six months, one, two and three years are described in Table 4.

Table 4: Uncorrected Visual Acuity (UCVA) of the Patient Population

Uncorrected Visual Acuity	Percent (%) of Subject at Each Visit			
	6 Month	1 Year	2 Year	3 Year
20/20 or better	33.2	35.1	34.6	31.2
20/40 or better	86.7	86.6	87.1	84.0
20/80 or better	97.9	97.8	98.3	95.2
Worse than 20/80	2.1	2.1	1.7	4.8
Number of Patients	581	493	356	231

Table 5: Percentage of the Patient Population Achieving Uncorrected Distance Visual Acuity (UCDVA) Where Emmetropia was the Goal and Preop Best Corrected Visual Acuity ≥ 20/20

Uncorrected Visual Acuity	Percent (%) of Subject at Each Visit	
	1 Year	3 Year
20/20 or better	47.1	44.3
20/40 or better	93.6	92.0
20/80 or better	100.0	97.7
Worse than 20/80	0.0	2.3
Number of Patients	204	88

Uncorrected distance visual acuity (UCDVA) over time for first eyes targeted for emmetropia (± 0.50 D) is show in Table 5. For the primary analysis group, at one year, 93.6% of eyes achieved 20/40 or better UCDVA; at three years, 92.0%.

Table 6: Best Corrected Visual Acuity (BCVA) of the Patient Population During the Study

Uncorrected Visual Acuity	Percentage (%) of Patients at Each Visit			
	6 Month	1 Year	2 Year	3 Year
20/20 or better	78.1	78.7	82.8	78.9
20/40 or better	100.0	99.6	100.0	100.0
20/80 or better	100.0	100.0	100.0	100.0
Worse than 20/80	0.0	0.0	0.0	0.0
Number of Patients	580	493	355	228

The best corrected distance visual acuity over time for the primary analysis group is summarized in Table 6. As of six-month postoperatively, 100% of eyes achieved 20/40 or better BCVA through three years. At one year, 99.6% (491/493) of eyes achieved 20/40 or better BCVA; at two years, 100.0% (355/355); and, at three years, 100% (228/228).

Table 7: Best Corrected Visual Acuity of the Patient Population During the Study – Eyes with Preoperative BCVA 20/20 or Better

Uncorrected Visual Acuity	Percentage (%) of Patients at Each Visit			
	6 Month	1 Year	2 Year	3 Year
20/20 or better	93.6	95.1	96.6	95.3
20/40 or better	100.0	100.0	100.0	100.0
20/80 or better	100.0	100.0	100.0	100.0
Worse than 20/80	0.0	0.0	0.0	0.0
Number of Patients	342	288	207	127

For those eyes with preoperative BCVA of 20/20 or better, BCVA over time for eyes in the primary analysis group is summarized in Table 7. As of six months, 100.0% (342/342) of subjects with a preoperative BCVA of 20/20 or better achieved 20/40 or better postoperatively.

Table 8: Manifest Refraction Spherical Equivalent Distribution During the Study

Plano to:	Percentage (%) of Patients at Each Visit		
	1 Year	2 Year	3 Year
± 0.5 D	72.0	73.8	71.7
± 1.0 D	94.5	93.8	94.7
± 2.0 D	98.2	98.3	97.8
> 2.0 D	1.8	1.7	2.2
Number of Patients	492	355	226

The majority of eyes (71.7% to 73.8%) had manifest refraction spherical equivalent (MRSE) within ± 0.50 D of target; a larger majority of eyes (93.8% to 94.7%) had MRSE within ± 1.0 D of target (Table 8). The MRSE change between visits for the primary analysis group is summarized in Table 9. The mean MRSE change between

consecutive visits is less than -0.1 D with the most change occurring between the two and three year visits (-0.062 D). The majority of eyes (82.5% to 85.4%; Table 10) achieved within ± 0.50 D of change in MRSE between consecutive visits and a larger majority (95.9% to 97.9%) achieved within ± 1.0 D of change in MRSE between visits.

Table 9: Mean Spherical Equivalent Change Between Visits

Spherical Equivalent	Period		
	6 months – 1 year	1-year – 2 year	2-year – 3 year
Mean	-0.019	-0.058	-0.062
Std. Dev.	0.47	0.48	0.48
Maximum	-2.12	-4.25	-1.37
Minimum	2.37	2.00	3.12
C.I.	0.041	0.050	0.063
Number of Patients	485	349	215

Table 10: Manifest Refraction Spherical Equivalent Change in Patient Population Between Visits

Plano to:	Percentage (%) of Patients by Period		
	6 months – 1 year	1-year – 2 year	2-year – 3 year
± 0.5 D	82.9	85.4	82.5
± 1.0 D	97.1	97.7	95.9
± 2.0 D	99.6	99.7	99.5
> 2.0 D	0.4	0.3	0.5
Number of Patients	485	349	215

From a patient satisfaction survey with at least one-year follow-up, the majority reported no night visual symptom change in night glares (73.6%; 273/371), halos (72.0%; 268/372) and starburst (78.5%; 292/372) at night. For patients with night visual symptoms changes, there was a correlation with refractive cylinder and halos at night (28% (104/372); p value = 0.002). There was no significant correlation between the lens power and night visual symptom changes or any correlation between the lens optic sizes being smaller than some patients' mesopic pupil size. A contrast sensitivity substudy (n=31) concluded that there was no decrease in contrast sensitivity under mesopic and photopic conditions for patients implanted with the phakic IOL.

Table 11: Key Safety Variables at 2-Year Stratified by Preoperative MRSE (Eyes implanted 3 or More Years)

Lens Power (Diopter)	All Eyes – affected eyes/total eyes (n/N)			Preop BCVA 20/20 or better Eyes* -n/N
	Loss ≥ 2 lines BSCVA	BSCVA worse than 20/40	Increase > 2 D Cylinder	BCVA Worse than 20/25
-5.0	0/5	0/5	0/5	0/4
-6.0	0/19	0/19	1/19	0/17
-7.0	0/22	0/22	0/22	0/16
-8.0	1/32	0/32	0/32	0/30
-9.0	1/64	0/64	0/64	1/52
-10.0	0/56	0/56	0/56	0/41
-11.0	0/63	0/63	0/63	0/42
-12.0	0/74	0/74	0/74	0/56
-13.0	0/61	0/61	0/61	0/35
-14.0	0/59	0/59	0/59	0/28
-15.0	0/49	0/49	0/49	0/21
-16.0	0/27	0/27	0/27	0/10
-17.0	0/16	0/16	0/16	0/4
-18.0	0/21	0/21	0/21	0/6
-19.0	0/16	0/16	2/16	0/3
-20.0	0/7	0/7	0/7	0/0

*Contact lens or spectacles were used to determine visual acuity.

Table 12: Treatment Induced Astigmatism in Patient Population

Visit	Percentage (%) patient with refractive cylinder change >2.0D	First eyes treated
1 year	2.4	492
2 year	2.0	355
3 year	3.5	226

Table 11 stratifies the key safety variable at two years by preoperative MRSE. In the study, 2.0% to 3.5% of the treated first eyes experienced refractive cylinder change greater than 2.0 D (Table 12). The study safety target was <5%. In the study, the cumulative incidence of lens opacity was 4.5% (49/1088 eyes). The majority of these opacities were not visually significant and the cumulative incidence includes enrolling eyes with pre-existing opacities under a protocol exemption process. During the study, four opacities were determined to be visually significant and three required extraction. One of the subjects with lens opacities lost 2 lines of BSCVA. The rate of cataract surgery in the general population for greater than 40 years of age is 1.7% to 10.8%.

The endothelial cell density was collected with Konan specular microscopes from 12 sites. The endothelial cell number was counted at one reading center and the study population consisted of 353 eyes from 215 subjects. ARTISAN® Phakic IOL

implanted eyes with anterior chamber depths less than 3.2 mm exhibited the greatest cumulative endothelial cell loss (9%) at three years (see Table 13). The highest rate of endothelial cell loss (2.37%) was experienced between the second and third year (Table 14). The lowest rate of endothelial cell loss (0.4%) was experienced from baseline to 6 months. This is noteworthy as patients treated for cataract removal and IOL implantation surgery generally experience an average endothelial cell loss of 10% from ocular trauma.

Table 13: Percent Cumulative Endothelial Cell Loss for Various Anterior Chamber Depths from 6-Month to 3-Year

Anterior chamber depth	Cumulative Cell Loss (%)	Number of Patients
3.0 mm to 3.1 mm	9.0	7
≥3.2 mm to 3.4 mm	2.9	22
>3.4 mm to 3.9 mm	4.1	51
>3.9 mm	6.3	31

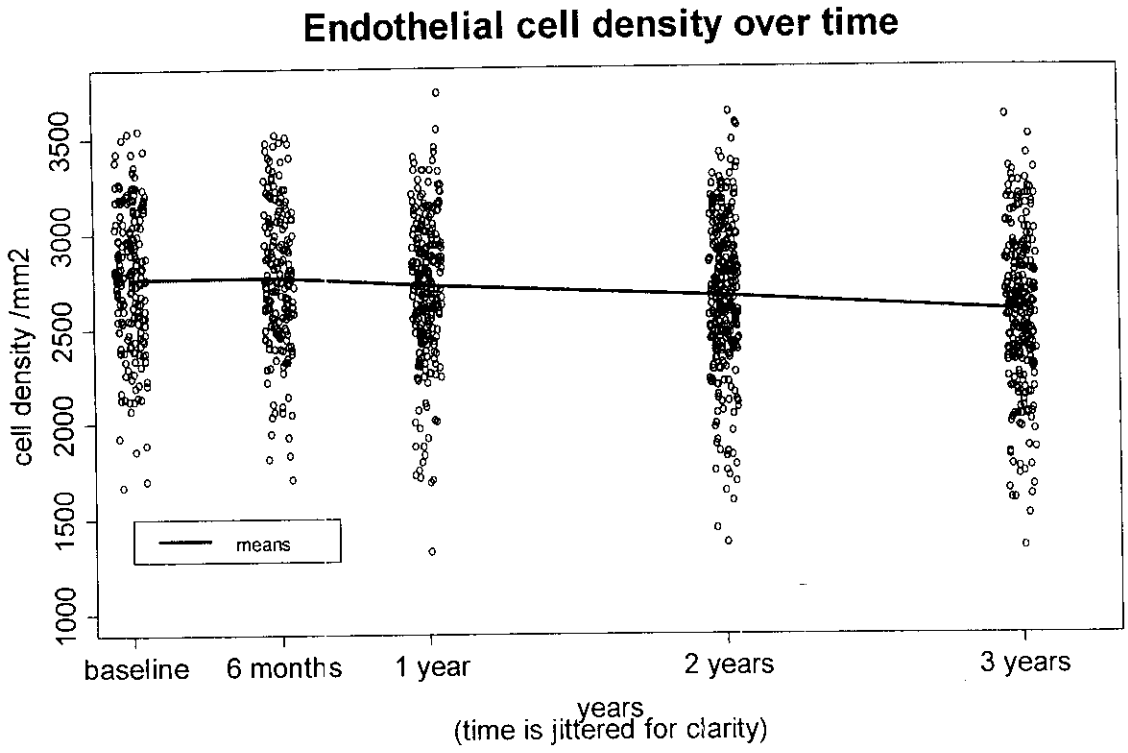
Table 14: Percent Loss in Endothelial Cell Density by Period

Period	% Cell Change (± SD)	Lower 95% CI**	Number of Patients
0 to 6 month	-0.40 (7.8)	-1.58	139
6 month to 1 year	-1.17 (6.2)	-2.17	149
1 year to 2 year	-1.12 (5.8)	-1.92	198
2 year to 3 year	-2.37 (6.3)	-3.22	216
6month to 3 year	-4.75 (7.3)	-6.10	111

Mean endothelial cell density results for a consistent cohort group of 57 eyes with useable data available at postoperative visits are shown in the Table 15.

Table 15: Endothelial Cell Density for a Consistent Cohort

Visits	Mean	Std. Dev.	Std. Error	95% Confidence Limits	
PreOp	2818.33	425.01	56.29	2708.00	2928.67
0.5 year	2812.86	465.79	61.70	2691.94	2933.78
1.0 year	2768.25	460.42	60.98	2648.72	2887.77
2.0	2760.26	478.54	63.38	2636.03	2884.50
3.0	2692.98	478.64	63.40	2568.73	2817.24



The rate of endothelial cell density loss in implanted eyes is 1.8% with an upper 90% confidence limit of 2.31% (if eyes with anterior chamber depth less than 3.2 mm are excluded). The rate of endothelial cell loss was determined from a regression analysis that included the data from all subjects with two or more measurements excluding the preoperative measurement. Stratified analyses of the endothelial cell loss data demonstrated no consistent statistically significant association with gender, age, lens model, and preoperative MRSE.

The following table shows the postoperative outcomes by proportion compared to preoperative levels for glare, halos, and starbursts, etc., stratified by the mesopic pupil sizes measured preoperatively.

Visual Symptoms	Pupil Size (mm)	Subjects Response to Questionnaire*		
		Percent with no change in symptoms preop to postop	Change in symptoms preop to postop	
			Percent Preop NO, Postop YES	Percent Preop YES, Postop NO
Glare	All	73.6	13.5	12.9
	≤4.5	70.4	14.3	15.3
	>4.5 to ≤5.5	71.6	13.4	15.1
	>5.5	76.3	16.8 (p=0.04)+	6.9
Starbursts	All	78.5	11.8	9.7
	≤4.5	77.8	12.1	10.1
	>4.5 to ≤5.5	74.5	16.3	9.3
	>5.5	81.2	10.9	7.9
Halos	All	72.0	18.2 (p=0.002)+	9.8
	≤4.5	72.8	17.2	10.1
	>4.5 to ≤5.5	69.2	19.2	11.6
	>5.5	72.2	23.8 (p.0.001)+	4.0

*412 subjects completed the questionnaire; data presented for those subjects that answered nighttime symptom questions; pupil size groups: ≤4.5 mm (n=99), >4.5 to 5.5 mm (n=172), >5.5 mm (N=101).
+Statistically significant (McNemar's Test) for those subjects reporting a change in symptom occurrence preoperatively to postoperatively.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

RISK BENEFIT ANALYSIS

The ARTISAN® Phakic IOL is surgically implanted in the eye to correct myopia. The lenses may eliminate the need for spectacle or contact lenses for some patients. The risks associated with eye surgery and this lens includes: retinal detachment, cataract, endophthalmitis (inflammation of the tissues inside the eyeball), raised intraocular pressure, uvetis (inflammation of any of the structures of the uvea: iris, ciliary body, or choroid) and corneal decompensation (typically related to endothelial cell loss). It is reasonable to conclude that the benefits of use of the lens for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

SAFETY

The anterior chamber ARTISAN® Phakic IOL's adverse events are comparable to or lower than the rates associated with the historical control population of standard posterior chamber monofocal IOLs with the following exceptions: retinal detachment, IOL dislocation and surgical reintervention. The 3-year data from the clinical study indicates a continual steady loss of endothelial cells of -1.8% per year and this rate has not been established as safe. If endothelial cell loss continues at the rate of 1.8% per year, 39% of patients are expected to lose 50% of their corneal endothelial cells within 25 years of implantation. The long-term effect on the cornea's health of a 50% loss in corneal endothelial cells is unknown. However, if too many cells are lost the patient may need a corneal transplant. Therefore, it is very important that the patient's endothelial cell density is periodically monitored.

EFFECTIVENESS

The ARTISAN® Phakic IOL met or exceeded the targeted effectiveness criteria for refractive stability, uncorrected visual acuity, best corrected visual acuity and refractive predictability.

XII. PANEL RECOMMENDATION

At an advisory meeting held on February 5, 2004, the Ophthalmic Devices Panel recommended the Ophtec PMA for the ARTISAN® Phakic IOL Models 204 and 206 be approved subject to the following conditions:

(1) Provide a detailed post-approval study to determine the adverse event rate of clinically significant events.

(2) Continue to follow for an additional two years the PMA cohort's endothelial cell density. (five years total follow-up)

(3) Provide a reanalysis of existing data with respect to pigment dispersion and intraocular pressure changes for the minority cohort subsets to include those patients with brown irides

(4) Provide a cumulative reanalysis of the adverse events and complications reported in your study on a per eye and per patient basis for the subsets and the overall group presented in your PMA.

(5) Modify the patient and physician labeling.

XIII. CDRH DECISION

The Center for Devices and Radiological Health (CDRH) concurred with the Panel recommendation of February 5, 2004, and issued an approval order on September 10, 2004. The applicant agreed to collect 5-year follow-up data to evaluate the vision threatening adverse events associated with the use of the ARTISAN® (also known as Verisyse™) intraocular lens in ≥2000 implanted eyes (from a 5000 eyes registry) and to continue to follow the PMA cohort's endothelial cell density for an additional two years. Additionally, the applicant provided the reanalyses listed above (#3 and #4) and CDRH found the data to be adequate. In regards to revising the patient's and physician's labeling, CDRH took the Panel's comments into consideration. The applicant's manufacturing facility was inspected on January 15, 2004 and was found to be in compliance with the Quality System Regulation (21 CFR 820).

Expedited review status was granted on August 13, 2003 for the following reason: we believe that the ARTISAN® Phakic IOL may provide a clinically meaningful advantage over existing technology in terms of increased effectiveness for some myopic patients.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

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